

## **REMARKS/ARGUMENTS**

Claims 1-28 are pending in the application. Claims 3, 6, 7, 13-21, and 24-26 are withdrawn. Claims 1, 2, 4, 5, 8-12, 22, 23, 27, and 28 are pending and presently stand rejected. New claims 29-31 have been added and are readable upon the elected species.

### **Rejection under 35 USC § 103**

Claims 1, 2, 4, 8, and 11 were rejected under 35 USC § 103(a) as being unpatentable over Hughes (1996 Tetrahedron Letters 37: 7595-7598) and Lough et al (US 5,900,481). Applicants respectfully disagree. First, not all elements of these claims are taught by the combined teachings of Hughes and Lough et al. In responding to Applicants' arguments, the Examiner contends that "features upon which applicant relies (i.e., cleavage of the onium salt) are not recited in the rejected claim(s)." Final Office Action, page 4. Applicants' arguments regarding a "ternary or quaternary onium group" in the first paragraph of page 9 of the amendment date stamped July 11, 2006 were in response to the rejection (now withdrawn) of claims 1 and 8 under 35 USC 102(b) as being anticipated by Lough. Applicants respectfully request clarification as to arguments made, if any, regarding features not in the claims under the rejection of claims 1, 2, 4, 8, and 11 under 35 USC § 103(a) as being unpatentable over Hughes (1996 Tetrahedron Letters 37: 7595-7598) and Lough et al (US 5,900,481).

Second, the Examiner asserts that "hydrolysis of Hughes' phosphonium salt produces a neutral phosphine oxide species, rather [than] recreating the triphenyl phosphine resin, as alleged by applicant" relying on a paper by Bernard and Ford (*J. Org. Chem.* (1983), 48, 326-332)) for

additional support. Final Office Action, page 3. This assertion is incorrect and improper on several grounds.

1. Applicants note that while Hughes describes a reaction of a polymer-supported phosphonium compound with sodium methoxide and methanol as a "hydrolysis" reaction, the fate of the polymer-supported phosphorus compound is not described. The Bernard reference does not concern such "hydrolysis" reactions, describing only the Wittig reaction which is known to produce a triarylphosphine oxide under the reaction conditions. No evidence is of record to support the Examiner's contention that the alleged hydrolysis reaction produces a "neutral phosphine oxide species."

2. Additionally, the characterization of the alleged triarylphosphine oxide as neutral is not the same as holding that the phosphorus center is neutral. The article being submitted with the enclosed Information Disclosure Statement [E.L. Wagner, *J. Am. Chem. Soc.* **85**, 161-164 (1963)] demonstrates that triarylphosphine oxides have a significant polar character having a polarized phosphorus-oxygen bond. Table III on page 163 of the reference depicts calculated charges on the P and O atoms of a series of phosphine oxide compounds. Triphenylphosphine oxide has a charge of +.842 and -.827 on P and O, respectively while trimethylphosphine oxide has charges of +1.03 on P and -1.132 on O. The best description for these compounds thus has a positive charge on the phosphorus atom and a negative charge on the oxygen atom. Applicants' wish to point out that the reference was not cited before because it was discovered after performing a search to refute a position that was newly raised by the examiner in the final rejection.

3. Moreover, Applicants dispute the Examiner's position that the combination of the silica beads of Lough combined with a polymeric phosphonium compound convertible by hydrolysis to a phosphine oxide in which the phosphorus is still appended to the solid polymer support "but lacks a positive charge for electrostatic attraction of a nucleic acid ... represents a cleavable linker portion linking the nucleic acid binding portion to the solid support." There simply is no showing in Hughes of a cleavable linker portion linking the nucleic acid binding portion to the solid support as recited in Applicants' claim 1.

4. The Examiner tries to characterize the conversion of a phosphonium salt group in Hughes to an allegedly neutral phosphine oxide by a bond cleavage reaction as an obvious equivalent of Applicants invention, alleging that the neutral phosphine oxide would not bind nucleic acid. This is entirely speculation and unsupported by any evidence. There can be no expectation of the success of a hypothetical material operating by a previously unknown and unproven principle. Applicants' independent claims 1 and 27-31 require the cleavable linker portion to link the nucleic acid binding portion to the solid support and further require that the nucleic acid binding portion include at least one of a ternary sulfonium group, a quaternary ammonium group, or a quaternary phosphonium group as recited in claim 1 and as varied in independent claims 27-31. If the phosphonium salt group of Hughes is the cleavable linker, then there is no separate nucleic acid binding portion in Hughes that would meet the requirements of Applicants' claims. That is, Hughes would only disclose one of the two separate claim elements. A single element in the prior art cannot meet the requirement of two separate elements in

Applicants' claims. When claim elements are missing in the prior art, no *prima facie* case of obviousness can be established.

5. The Examiner's description of the phosphonium salt of Hughes as a linker that may be substituted in the materials of Lough is at odds with the characterization of the phosphonium salt being used for "orthogonal nucleic acid binding." Office Action page 4. Applicant requested clarification in the previous response whether the phosphonium salt group was intended to be combined with the silica solid phase of Lough as a linker or a nucleic acid binding group. (1st response, page 10, paragraph 3) The present Office Action still does not clarify this point and seems to be taking both positions, depending on the point being made. Leading to further ambiguity, the original rejection was stated to "combine the chemistry developed by Hughes with the nucleic acid binding silica beads of Lough, et al." How this combination would be effected still has not been explained. The bond linking the phosphorus to the polymer support in Hughes is not severed, as admitted by the Examiner. Applicant can not determine what is to be linked with what, how it is then to be cleaved, and whether the phosphonium group is merely a linker. For example, is the phosphonium group intended to be the linker between the solid support and the bead or between the bead and the nucleic acid? Without a clear explanation, no *prima facie* case of obviousness has been established.

Finally, the Examiner rejects the argument that there is no motivation to combine Lough et al and Hughes. Final Office Action, page 4. While Applicants continue to dispute that there is any motivation to combine the teachings of Lough and Hughes, they point out that this combination would still not render the present claims obvious. The phosphonium group in the

present claims is a nucleic acid binding group not a bivalent linker group. There is no teaching or suggestion in either reference of the use of a phosphonium group for nucleic acid binding. In the Office Action the Examiner opines that orthogonal (nucleic acid) binding and orthogonal linking are intertwined concepts and that a motivation to combine the references based on the desirability of orthogonal linking means is akin to a motivation based on orthogonal binding means. Applicants maintain their disagreement with this view. Lough itself does not describe or contemplate orthogonal nucleic acid binding. Lough, in fact, not only does not disclose orthogonal nucleic acid binding, it does not disclose any materials for binding nucleic acids non-covalently and non-sequence specifically in the sense of the present claims. Lough is concerned with compositions comprising a bead conjugated to a solid support and further conjugated to a nucleic acid. The conjugation of bead and solid support is independent of and can occur despite the total absence of nucleic acid. Conjugation of bead and nucleic acid is separately described. Since there is no causal connection between the two instances of conjugation, it can not be held that linking a solid support to a bead is nucleic acid binding. It is acknowledged that different conjugation means between bead and nucleic acid are described, including covalent linkage and hydrophobic attraction. However all embodiments described or contemplated in Lough rely on modification of a specific nucleic acid by covalent attachment of the nucleic acid to either the bead or to another chemical entity such as a trityl group. In the latter embodiment it is the chemically attached trityl group which is attracted to the bead by virtue of its hydrophobic nature; the label would be bound even in the absence of nucleic acid. The nucleic acid is not capable of attraction or binding to the bead by itself. Thus all disclosed means for affixing a

nucleic acid to a bead are distinct from those presently claimed. As a further distinction, in all cases described in Lough a chemical reaction is required to regenerate the nucleic acids by freeing them from their covalent chemical attachments. In summary, the alleged motivation based on achieving orthogonal binding is refuted since no such concept is disclosed and any nucleic acid binding enabled by incorporating a phosphonium group taught in Hughes could not operate in the manner disclosed in Lough.

The arguments against the Examiner's interpretation notwithstanding, Applicants again state their belief that there could be no expectation of success of the proposed hypothetical material for the purposes of Lough using the chemistry of Hughes for the reasons stated above related to speculative chemistry not found in any references of record.

For the reasons explained, applicants maintain that no *prima facie* case of obviousness has been established, and the rejection of claims 1, 2, 4, 8, and 11 should be withdrawn.

#### Rejection under 35 USC § 112

Claims 1, 2, 4, 5, 8-12, 22, 23, 27, and 28 were rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the specification as originally filed provided no implicit or explicit support for "non-covalently and non-sequence specifically binding nucleic acids," as contained in claims 1, 27, and 28. Applicants respectfully disagree. As stated in MPEP 2173.05(i), "a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter.

1993).” In *Ex parte Parks*, the Board of Patent Appeals and Interferences reversed a rejection under the first paragraph of 35 USC § 112 for a lack of support for the claim limitation, “in the absence of a catalyst,” where the disclosure did not mention a catalyst because “it cannot be said that the originally-filed disclosure would not have conveyed to one having ordinary skill in the art that appellants had possession of the concept of conducting the decomposition step . . . in the absence of a catalyst.” 30 USPQ2d at 1236.

The “fundamental inquiry” with respect to the written description requirement “is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.” MPEP 2163.02. Moreover, the CCPA stated in a related context that “applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable.” *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90 (CCPA 1976). An applicant has the right “to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed.” *Id.*

Applicants maintain that it is readily understood from the disclosure and the worked examples that the binding of nucleic acids to the presently claimed materials is not dependent on recognition of a particular base sequence and does not occur by covalent bond formation between the nucleic acids and the presently claimed materials. These properties are inherent in the nature of the materials by virtue, at least, of the nature of the nucleic acid binding portion. The Examiner recognizes that ternary and quaternary onium groups function, at least in part, by electrostatic attraction of nucleic acids. It is known from references already of record, e.g. US

4,699,717; US 5,057,426; EP 124349, that quaternary ammonium groups bind DNA by this mechanism and do so noncovalently and non-sequence specifically. Moreover capture of nucleic acids by sequence recognition or covalent bond formation is nowhere disclosed in the present specification. The objected to terms merely represent inherent properties of the nucleic acid binding groups disclosed (ternary sulfonium group, quaternary ammonium, quaternary phosphonium group  $PR_3^+X^-$ ; and ternary sulfonium group of the formula  $SR_2^+X^-$  where R is selected from  $C_1$ - $C_{20}$  alkyl, aralkyl and aryl groups, quaternary ammonium group of the formula  $NR_3^+X^-$  where R is selected from  $C_4$ - $C_{20}$  alkyl, aralkyl and aryl groups, and quaternary phosphonium group of the formula  $PR_3^+X^-$  where R is selected from  $C_1$ - $C_{20}$  alkyl, aralkyl and aryl groups, and wherein X is an anion; and quaternary phosphonium group where the R groups each contain from 1-20 carbon atoms). In contrast to the Examiner's statement, noncovalent and non-sequence specific binding is certainly implicit in every worked example. For instance, examples 43 and 68 demonstrate the binding of genomic DNA containing a myriad of different sequences and lengths of nucleic acid. Other examples demonstrate binding of RNA or plasmid DNA. No covalent modification is involved and no sequence recognition is involved.

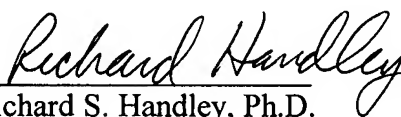
Because "the ternary or quaternary onium solid phase materials remain positively charged regardless of the pH of the reaction medium," application, page 12, lines 14-18, these groups have the ability to attract nucleic acids of a variety of lengths and sequences and bind them without covalent bonding and without sequence specific binding. For the reasons explained, applicants maintain that claims 1, 2, 4, 5, 8-12, 22, 23, 27, and 28 do comply with the



written description requirement, and the rejection under 35 USC § 112, first paragraph should be withdrawn.

This proposed amendment after final proposes to add new claims wherein the binding portion “consists essentially of at least one of a ternary sulfonium group, a quaternary ammonium, or a quaternary phosphonium group  $\text{PR}_3^+\text{X}^-$ ” in claim 29; and wherein the binding portion “portion consists essentially of a quaternary phosphonium group  $\text{PR}_3^+\text{X}^-$  wherein R is selected from  $\text{C}_1\text{-C}_{20}$  alkyl, aralkyl and aryl groups, and wherein X is an anion” in claims 30 and 31. Applicants believe these additional claims should not be objectionable.

For the reasons given, applicants respectfully assert that all grounds for rejection have been overcome and request Notice of Allowance.

  
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